University of Alberta

Effects of Timing of Adjuvant Treatment on Survival of Patients with Stage III Colon Cancer and Stage II/III Rectal Cancer in Alberta

by

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Dedication

I would like to dedicate this thesis to my dearly loved wife, Cecília, and my wonderful little daughter, Alice.

Abstract

Surgery followed by adjuvant treatment has been an evidence-based treatment recommendation for stage III colon cancer and stage II/III rectal cancer since 1990. Clinical trial results are, however, uninformative regarding the definitive outer limit by which adjuvant treatment should be received for optimal survival benefit. The purpose of my thesis research was to assess the effect that the timing of adjuvant therapy has on patient survival in actual clinical practice.

Residents of Alberta diagnosed with stage III colon adenocarcinoma and those diagnosed with stage II/III rectal adenocarcinoma in 2000-2005 who had surgery were included in the study. Patients were identified from the Alberta Cancer Registry.

Stage III colon cancer patients who received adjuvant chemotherapy 12-16 weeks after surgery, and 16 weeks or later after surgery or never received it, were more likely to die compared to those treated within 8 weeks (hazard ratio (HR)=1.68, 95% confidence interval (CI) 1.12-2.51, p-value=0.01, and HR=2.17, 95%CI 1.62-2.91, p-value<0.001, respectively).

The rectal-cancer-specific-mortality HR for patients who received adjuvant treatment 12 weeks or later after surgery, compared to those who received it within 8 weeks after surgery, was 1.40 (95%CI 0.89-2.21, p-value=0.15). Similarly, those who did not receive adjuvant treatment had a 60% increase in the hazard of rectum-cancer-specific mortality (95%CI 1.11-2.31, p-value=0.01), compared to those who received it within 8 weeks, adjusting for stage; neoadjuvant treatment status; sex; age at diagnosis; region of residence at

diagnosis; number of co-morbidities; year of diagnosis; and neighborhood-level socioeconomic factors.

Rectum cancer patients who did not receive adjuvant treatment also had a 1.72 times higher overall mortality hazard compared to those who received the treatment within 8 weeks after surgery (HR=1.72, 95%CI 1.26-2.37, p-value=0.001).

These results should be communicated to oncologists and discussed towards system changes that improve the receiving and timing of adjuvant therapy for these cancer patients.

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List of Abbreviations

ACCS = Ambulatory Care Classification System

AJCC = American Joint Committee on Cancer

CI = Confidence interval

CRC = Colorectal cancer

DAD = Discharge Abstract Database

FGSR = Faculty of Graduate Studies and Research

HR = Hazard Ratio

ICD-O = International Classification of Diseases for Oncology

NIH = National Institute of Health

P = P-value

TNM System = Tumor, Node, and Metastasis System

US = United States

Chapter 1: Introduction

1.1 Thesis Organization

This is a paper-format thesis prepared in accordance with the Faculty of Graduate Studies and Research (FGSR) guidelines, University of Alberta. The thesis is organized as follows:

Chapter 2 – First Manuscript[1]: *Effects of Timing of Adjuvant Chemotherapy on Survival of Patients with Stage III Colon Cancer in Alberta*

Chapter 3 – Second Manuscript[2]: *Timing of Adjuvant Treatment and Survival in Patients with Stage II/III Rectal Cancer in Alberta*

Chapter 4 – Discussion and Conclusions

[1] A version of Chapter 2 has been submitted to *Cancer* for publication.
[2] A version of Chapter 3 has been submitted to *JAMA* for publication.

1.2 Rationale

Colorectal cancer (CRC) refers to the cancer originated in the colon or rectum. About half of the patients diagnosed with CRC still die due to the cancer, even though nearly 75% of the individuals diagnosed undergo a primary surgical resection and there have been numerous improvements in therapy (1). CRC is a major public health burden in Canada. It is the third most frequent type of cancer in incidence (2). It is the second leading cause of cancer death among males and the third among females in Canada (2).

In the early 1990's, the United States (US) National Institute of Health (NIH) consensus conference developed treatment guidelines for patients diagnosed with CRC. The US NIH established surgical resection of the tumor followed by adjuvant chemotherapy as the guideline treatment for patients diagnosed with stage III colon cancer. In addition, the treatment guidelines for stage II/III rectal cancer consist of surgical resection of the tumor followed by adjuvant chemoradiotherapy (chemotherapy and radiotherapy) (3-5).

These guidelines were based on a large randomized trial conducted in the United States that showed a relative risk reduction of 33% for mortality and 40% for recurrence in stage III colon patients who received adjuvant chemotherapy compared to those who received surgery alone (6). The majority of the patients included in these trials initiated the adjuvant chemotherapy within 6 weeks after surgery. Therefore, it is not known whether the treatment is equally beneficial after this point in time.

In fact, several studies have found that a large proportion of surgically resected patients do not receive adjuvant treatment or experience treatment delays (7-11). In real clinical settings, there are several factors that may lead to delay in receipt of adjuvant treatment; this delay may adversely affect cancer recurrence and patients' survival.

A recent population-based study conducted with stage III colon adenocarcinoma in the United States, in fact, found that those who initiated adjuvant chemotherapy three months after surgery or later were associated with a 50% increase in colon cancer-specific mortality risk compared to those who initiate chemotherapy within one month (12).

In Alberta, the recommendations for stage III colon cancer patients are to receive adjuvant chemotherapy within twelve weeks of surgery (13). Based on recent study findings (12), this interval needs to be evaluated carefully. **Chapter 2** of this thesis will investigate and discuss the distribution of the timing of adjuvant chemotherapy after surgery and assess whether the timing of adjuvant chemotherapy has affected the survival of patients diagnosed with stage III colon cancer in Alberta between 2000 and 2005.

To our knowledge, no clinical trial or observational study has been conducted in North America that investigated the association between timing of adjuvant treatment initiation after surgery and survival among stage II/III rectal cancer patients. **Chapter 3** aims to quantify the proportion of patients receiving adjuvant treatment within 12 weeks of surgery, their clinical characteristics associated with delayed treatment, and to determine whether there is any

relationship between the timing of adjuvant treatment initiation and the survival of patients diagnosed with stage II/III rectal cancer.

1.3 Purposes

The overall purpose of this research was to investigate potential associations between the timing of adjuvant therapy initiation and survival for patients diagnosed with stage III colon cancer, or stage II/III rectal cancer in Alberta between 2000 and 2005.

1.4 Research Questions

Chapter 2:

1) What is the proportion of patients receiving adjuvant chemotherapy within 12 weeks after surgery, consistent to the provincial guideline?
2) What are the patient and clinical factors associated with receipt of timely adjuvant chemotherapy?
3) What is the relationship between the timing of initiation of adjuvant chemotherapy and survival for patients diagnosed with stage III colon cancer in Alberta between 2000 and 2005?

Chapter 3:

1) How are patients distributed across different treatment regimens (surgery only, neoajuvant treatment only, adjuvant treatment only, and neo + adjuvant treatment); and what are the patient and clinical factors associated with each treatment?
2) What is the proportion of patients receiving adjuvant treatment within 12 weeks after surgery, consistent with the provincial guideline?
3) What are the patient and clinical characteristics associated with the receipt of adjuvant treatment within 12 weeks after surgery?
4) Determine the relationship between the timing of adjuvant treatment initiation and survival of patients diagnosed with stage II/III rectal cancer in Alberta.

5) Determine the association between neoadjuvant treatment status and survival of patients diagnosed with stage II/III rectal cancer in Alberta.

1.5 Hypotheses

We expect to find associations between the timing of adjuvant treatment initiation after surgery and patient survival. The primary hypotheses of this thesis were as follows:

Hypothesis 1 (Chapter 2)

- Those who have received adjuvant chemotherapy 8-12 weeks after surgery will have similar survival probabilities as patients who received it within 8 weeks.
- Patients who have received adjuvant chemotherapy 12-16 weeks after their surgery will be associated with higher hazard of both overall and colon cancer-specific mortality, compared to patients who initiated adjuvant chemotherapy within 8 weeks after their surgery.
- Patients who have received adjuvant chemotherapy 16 weeks or later after their surgery, or never received it will be associated with higher hazard of both overall and colon cancer-specific mortality, compared to patients who initiated adjuvant chemotherapy within 8 weeks after their surgery.

Hypothesis 2 (Chapter 3)

- Patients who initiated adjuvant treatment 8-12 weeks after surgery will have similar survival patterns as patients who received it within 8 weeks.
- Patients who have received adjuvant treatment 12 weeks or later after their surgery will be associated with higher hazard of both overall and rectal cancer-specific mortality, compared to patients who initiated adjuvant treatment within 8 weeks after their surgery.
- Those who have never initiated adjuvant treatment after their surgery will be associated with an increase in overall and rectal cancer-specific mortality, compared to patients who initiated adjuvant treatment within 8 weeks after surgery.
- Patients who received neoadjuvant treatment will be associated with a decrease in overall and rectal cancer-specific mortality, compared to those who did not receive neoadjuvant treatment.

1.6 References

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Chapter 2: Effects of Timing of Adjuvant Chemotherapy on Survival of Patients with Stage III Colon Cancer in Alberta

2.1 Introduction

In the early 1990's, guidelines were developed that recommended patients with stage III colon cancer receive chemotherapy after their surgery (i.e., adjuvant chemotherapy) (1). These guidelines were based on large randomized studies conducted in the United States that showed a relative risk reduction of 33% for mortality and 40% for recurrence in patients who received adjuvant chemotherapy compared to those who received surgery alone (2). A large population-based study conducted in the United States with stage III colon cancer patients recently reported that adjuvant chemotherapy initiated three months after surgery or later is associated with a 50% increase in colon cancer-specific mortality, compared to those who initiate chemotherapy within one month (3). The guideline treatment for stage III colon cancer in Alberta consists of surgery followed by adjuvant chemotherapy initiated within 12 weeks from the date of surgery (4).

Regardless of the benefits and survival advantage gained by adjuvant chemotherapy, several studies have found that a large proportion of patients do not receive it or experience treatment delays (5-9).

The goals of this study are to: 1) quantify the proportion of patients receiving adjuvant chemotherapy within 12 weeks after surgery; 2) identify factors associated with receipt of timely adjuvant chemotherapy; and 3) quantify the relationship between the timing of initiation of adjuvant chemotherapy and

survival for patients diagnosed with stage III colon cancer in Alberta between 2000 and 2005.

2.2 Methods

2.2.1 Inclusion Criteria

All residents of Alberta who were diagnosed with stage III colon adenocarcinoma (International Classification of Diseases for Oncology (ICD-O) (10) code c18, c18.2- c18.9) between 2000 and 2005 who received surgery were identified from the Alberta Cancer Registry. Patients were excluded if they died within one week of their diagnosis, were diagnosed with another primary cancer within 6 months prior or subsequent to their colon cancer diagnosis, did not have a histologically confirmed disease, or were treated outside of Alberta. Cancer staging was based on the American Joint Committee on Cancer (AJCC version 6) (11).

2.2.2 Data Sources

Data were linked from the Alberta Cancer Registry, Ambulatory Care Classification System (ACCS), Discharge Abstract Database (DAD), and the 2001 Canadian census. The Alberta Cancer Registry, a member of the North American Association of Comprehensive Cancer registries, was established in 1942 and is responsible for recording and maintaining data on all cancer cases and cancer deaths occurring in Alberta; physicians and hospitals are legally required to report all cancer cases to the Alberta Cancer Registry. Patient demographics,

tumor histology and stage, postal code of residence at diagnosis, initial treatment modalities and start dates, and date of death were obtained from the Alberta Cancer Registry.

The ACCS and DAD databases contain diagnosis and procedure codes on all outpatient and inpatient hospital visits in the province of Alberta. All hospital visits that occurred in the year prior to the patient's cancer diagnosis were used to identify co-morbidities using an enhancement to the Charleson Comorbidity Index (12). Co-morbidity scores were categorized into three groups: no serious co-morbidity; one serious co-morbidity; and two or more serious co-morbidities.

The 2001 Canadian census was used to obtain socioeconomic indicators at the geographical level for each patient, also called the dissemination area (a neighborhood with approximately 600 households). Four variables were used as measures of the neighborhood socioeconomic status: 1) median income; 2) proportion of employment; 3) proportion separated, divorced or widowed; and 4) proportion not graduated from high school.

2.2.3 Statistical Analysis

Exploratory data analysis was performed to determine cut-offs for categorical variables. Descriptive statistics were calculated for the overall cohort with respect to patient and clinical characteristics. Chi-square or Fisher's Exact tests, as appropriate, were used to assess associations between patient/clinical characteristics and the timing of receiving chemotherapy (within 12 weeks versus more than 12 weeks versus not receiving chemotherapy). Patient and clinical

characteristics evaluated included: sex; age at diagnosis; region of residence at diagnosis; neighborhood socioeconomic factors; number of co-morbidities; and year of diagnosis.

Time from the date of surgery to the date of first chemotherapy session was calculated and patients were categorized into the following four groups for survival analysis: received chemotherapy within 8 weeks after surgery; 8-12 weeks after surgery; 12-16 weeks after surgery; or greater than 16 weeks or never received it. The last group was originally separated into "Received chemotherapy greater than 16 weeks" and "Never received chemotherapy." In the final analysis, these groups were combined because there was little difference between them. The final categories were used to evaluate whether a shorter or longer time than the currently recommended 12 weeks may be a more appropriate recommendation.

Kaplan-Meier curves were used to describe the patient survival stratified by time from surgery to adjuvant chemotherapy. Cumulative incidence curves were used to describe the cumulative mortality due to colon cancer-specific deaths, treating the other causes of death as competing risk (13). The Kaplan-Meier and cumulative incidence curves were started at 16 weeks after surgery. This starting time is the earliest time point that allows all “time from surgery to adjuvant chemotherapy” groups to be defined before the starting time: deaths prior to this starting time were not included in the analysis.

Cox proportional hazards models were used to estimate the adjusted colon cancer-specific and overall mortality hazard ratios (HR) by time from surgery to

adjuvant chemotherapy (time dependent covariate), starting at 16 weeks after surgery. The following covariates were included in the Cox regression models to produce adjusted HR estimates: sex; age at diagnosis; region of residence at diagnosis; number of co-morbidities; year of diagnosis; and neighborhood-level socioeconomic factors. In order to closely adjust for age at diagnosis, a natural cubic spline of age at diagnosis was used with four knots (14). Patients were followed to the earlier of death or March 31, 2009.

Some stage III colon cancer patients die soon after surgery and do not have an opportunity to receive chemotherapy. These patients are included in the group, did not receive chemotherapy, and improperly increase its HR of death. A sensitivity analysis was, therefore, conducted to assess whether changing the start time (T0) would result in different HR estimates for the timing of adjuvant chemotherapy on survival. Four different time points for T0 were considered in the sensitivity analysis: date of surgery; 12 weeks post-surgery; 16 weeks post-surgery; and 24 weeks post-surgery. We present the results with the earliest T0 (16 weeks) that produced HR estimates consistent with those using later start times for patients who did not receive adjuvant chemotherapy, the group that is most affected by early deaths.

All statistical analyses were conducted using SAS statistical software version 9.2 (SAS Institute, Cary, NC, USA) and R version 2.9 (R Foundation for Statistical Computing, Vienna, Austria).

2.3 Results

There were 1,211 residents of Alberta diagnosed with stage III colon cancer between 2000 and 2005. The following patients were excluded from the study: 20 patients who died within one week of their diagnosis; 52 patients diagnosed with another cancer within six months prior or subsequent to their diagnosis; six patients without a histological confirmation of the disease; 14 patients with a histology other than adenocarcinoma; two patients without a surgery; and one patient treated outside of Alberta. The remaining 1,116 patients were included in the study.

Table 2.1 shows the demographic, clinical, and neighborhood characteristics of the 1,116 patients included in the study stratified by time from surgery to the receipt of adjuvant chemotherapy. It also shows the proportion of patients who received treatment and the proportion who died during the study follow-up. Overall, 675 (60%) of the stage III colon cancer patients received adjuvant chemotherapy and 48% died. Patients aged 65 years and older and patients with co-morbidities were less likely to receive adjuvant chemotherapy. Patients who received chemotherapy more than 12 weeks post-surgery were more likely to live in neighborhoods with a high percentage of divorced, separated or widowed, a low employment rate, and a low median household income. In addition, this group had more co-morbidities compared to patients who received adjuvant chemotherapy within 12 weeks of surgery. The Edmonton area had the highest proportion of patients who received adjuvant chemotherapy within 12 weeks after surgery.

Figures 2.1 and 2.2 show the Kaplan-Meier and cumulative incidence curves for the overall survival and colon cancer-specific mortality, respectively, by time from surgery to adjuvant chemotherapy. The risk of death is greater for patients who received adjuvant chemotherapy more than 12 weeks post-surgery compared to those who received it within 12 weeks post-surgery for both overall and colon cancer-specific mortality.

Table 2.2 shows the adjusted mortality HRs and corresponding 95% confidence intervals (overall and colon cancer-specific) for patients with stage III colon cancer by timing of adjuvant chemotherapy. There was no difference in the overall or colon cancer-specific mortality hazard for patients who received chemotherapy 8 to 12 weeks post-surgery, compared to those who received it within 8 weeks after surgery. Patients who received adjuvant chemotherapy 12 to 16 weeks after surgery had a 1.68 times higher mortality hazard compared to those who received the treatment within 8 weeks (HR=1.68, 95% confidence interval (CI) 1.12-2.51). The same treatment group, although not statistically significant, was associated with a 32% increase in the hazard of colon cancer-specific mortality (HR=1.32, 95% CI 0.83-2.09). Patients who received adjuvant chemotherapy in week 16 or later or never received it had more than a two-fold hazard of death in comparison to those who received it within 8 weeks (HR=2.17, 95% CI 1.62-2.91), and had an 84% increase in the hazard of colon cancer-specific mortality (HR=1.84, 95%CI 1.33-2.55). All adjusted HR estimates were based on survival time T0=16 weeks post-surgery.

2.4 Discussion

The aims of this study were to identify the distribution of the timing of adjuvant chemotherapy from surgery, identify factors associated with the receipt of timely adjuvant chemotherapy, and to determine whether the timing of adjuvant chemotherapy was related to the survival of patients diagnosed with stage III colon cancer in Alberta.

The majority of patients 75 years or older and patients with two or more serious co-morbidities did not receive adjuvant chemotherapy (76% and 78%, respectively). Clinical trials and observational studies, however, have shown that older patients and those with co-morbidities benefit from adjuvant chemotherapy (15-18). Gross *et al*. found that, based on 5-year survival, the benefit of adjuvant chemotherapy does not change, regardless of the number of chronic health conditions a patient has (19). Another study that surveyed a nationally representative sample of 1,000 general surgeons and 1,000 oncologists in the United States found that both types of physicians hesitate to recommend adjuvant chemotherapy to patients older than 72 years old or with co-morbidities who have stage III colon cancer (20).

A study similar to ours that used the National Cancer Institute's Surveillance, Epidemiology, and End Results cancer registry data also found that receipt of chemotherapy 12 weeks post-surgery is the outer limit at which the maximum survival benefit of adjuvant chemotherapy is reached.

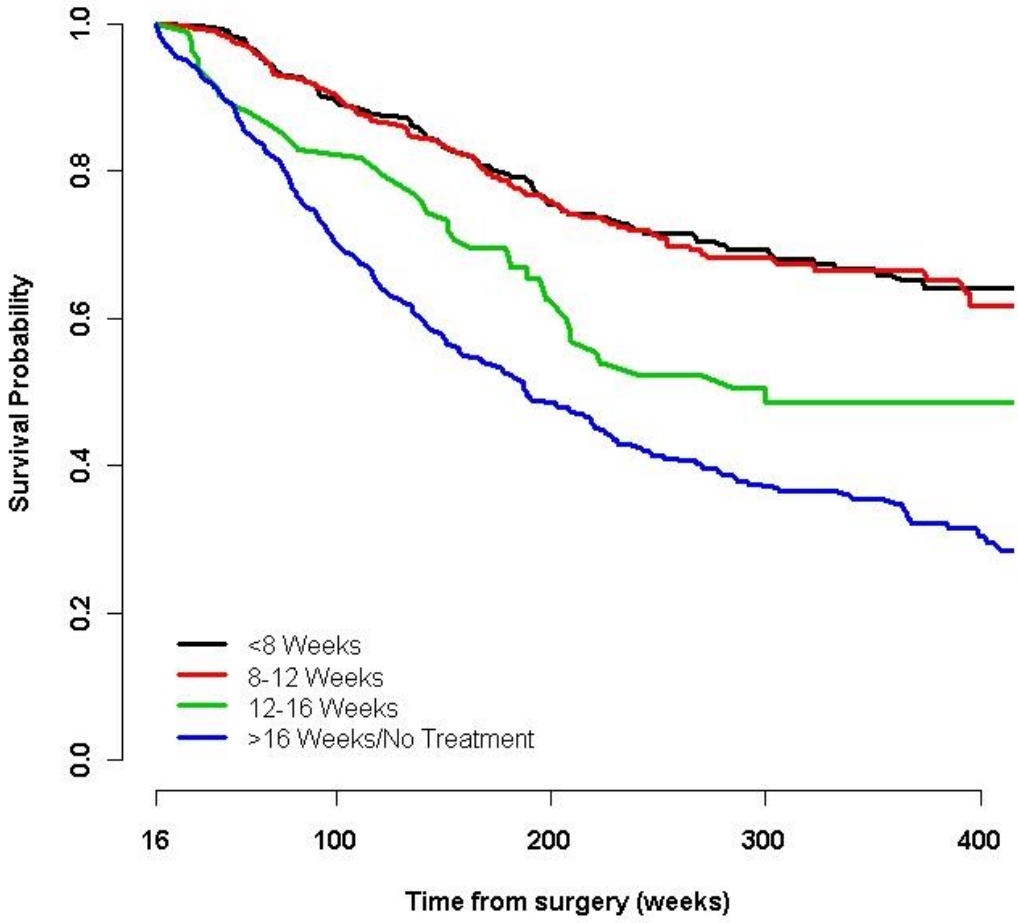
In Alberta, the treatment guideline for patients with stage III colon cancer state that adjuvant chemotherapy should begin within 12 weeks after surgery (4). Our results support these guidelines. A large portion of patients (40%), however, did not receive adjuvant chemotherapy or received delayed treatment. Investigation to identify the reasons for this is needed to optimize patient outcomes. The physician may delay chemotherapy due to slow recovery from surgery, post-surgery complications, or possibly a change in the patient's decision to receive adjuvant chemotherapy. Alternatively, delays may occur due to inefficiencies in the health care system or shortages of resources to deliver care. The variation in treatment by geographical regions is consistent with the latter possibilities. Further efforts are needed, however, to identify the key barriers to timely care.

The strengths of this study are that it is population-based and includes all patients diagnosed in the province of Alberta over a six-year period with four to nine years of follow-up. These strengths make the findings robust and generalizable. Limitations to the study, however, are that we did not have treatment details, such as completeness of the regimen or the specific chemotherapy regimens received. Other factors that were unavailable and could also effect patient survival were surgical complications and patient's functional status. This limitation was addressed to some extent, however, in the survival analysis by starting the survival time at 16 weeks post-surgery. This approach prevented potential over-estimation of HRs for those who received treatment 16 weeks or later or never received it by excluding those who died soon after

surgery. These people probably did not have the opportunity to receive adjuvant chemotherapy due to poor health post-surgery and probably would not have benefited from it. Thus, our HR estimates are on the conservative side.

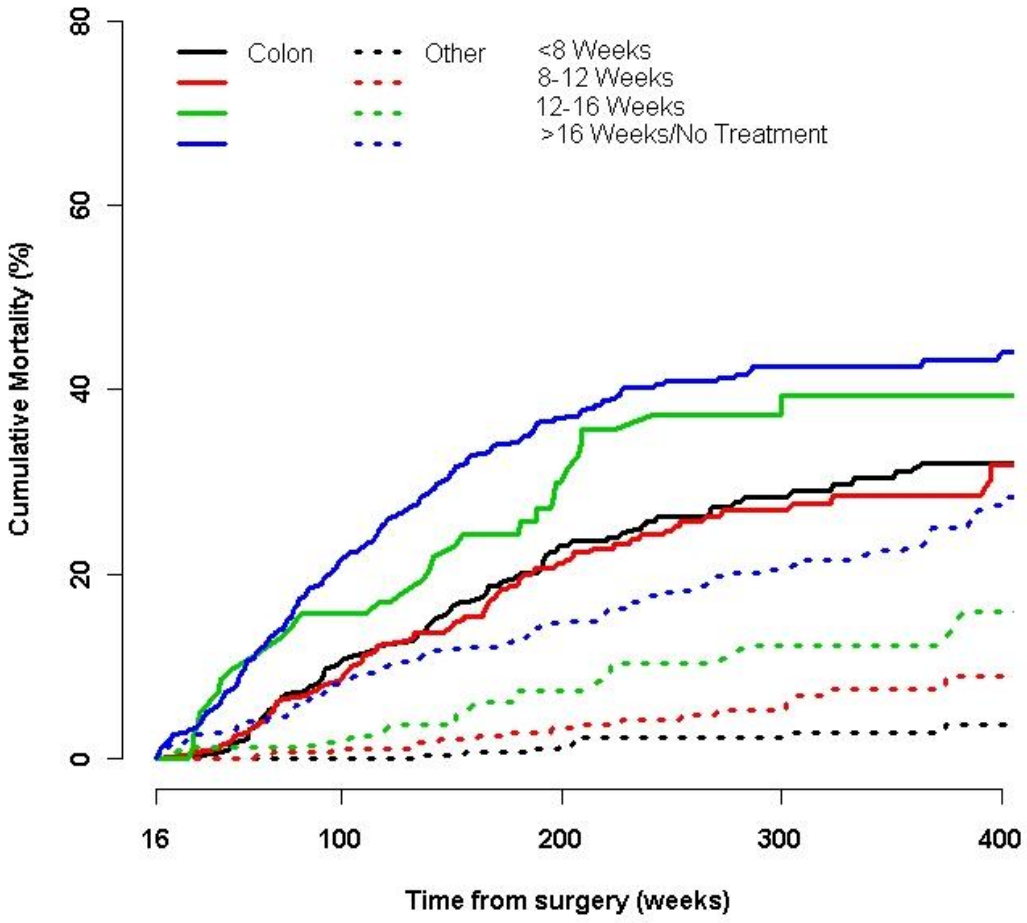
In conclusion, the results of our study support the current guidelines for treatment of stage III colon cancer in Alberta: surgery plus adjuvant chemotherapy should begin within 12 weeks after surgery. Forty-nine percent of the patients diagnosed between 2000 and 2005, however, did not receive chemotherapy or did not receive it within 12 weeks after surgery. Efforts are needed to improve uptake and initiation of adjuvant chemotherapy within 12 weeks after surgery in order to maximize the survival of patients with stage III colon cancer.

Figure 2.1: Kaplan-Meier Curves for the Overall Survival of Stage III Colon Cancer Patients by Time from Surgery to Adjuvant Chemotherapy



Note: Time from surgery to adjuvant chemotherapy starts at 16 weeks after surgery.

Figure 2.2: Cumulative Incidence Curves for the Colon Cancer-Specific Mortality by Time from Surgery to Adjuvant Chemotherapy



Note: Time from surgery to adjuvant chemotherapy starts at 16 weeks after surgery.

Table 2.1: Characteristics of Patients with Stage III Colon Cancer in Alberta with Respect to Receiving Adjuvant Chemotherapy and their Mortality

Patients' Characteristics	Total N (%[1])	Time to Adjuvant Chemotherapy N (%[2])			Patients who died N (%[2])
		≤ 12 Weeks	> 12 weeks	No treatment	
Total	**1116 (100)**	**572 (51)**	**103 (9)**	**441 (40)**	**538 (48)**
Sex*					
Female	539 (48)	258 (48)	45 (8)	236 (44)	263 (49)
Male	577 (52)	314 (54)	58 (10)	205 (36)	275 (48)
Age at diagnosis***					
<65 years	393 (35)	317 (81)	44 (11)	32 (8)	127 (32)
65 - 75 years	291 (26)	172 (59)	37 (13)	82 (28)	133 (46)
≥75 years	432 (39)	83 (19)	22 (5)	327 (76)	278 (64)
Residence at diagnosis***					
South	110 (10)	50 (45)	3 (3)	57 (52)	65 (59)
Calgary & area	353 (32)	177 (50)	49 (14)	127 (36)	162 (46)
Central	183 (16)	91 (50)	20 (11)	72 (39)	102 (56)
Edmonton & area	365 (33)	203 (56)	20 (5)	142 (39)	158 (43)
North	105 (9)	51 (49)	11 (10)	43 (41)	51 (49)
%Divorced, separated or widowed***					
<13% d/s/w	351 (32)	216 (62)	30 (9)	105 (30)	156 (44)
13% - 29% d/s/w	641 (57)	323 (50)	60 (9)	258 (40)	299 (47)
≥29% d/s/w	124 (11)	33 (27)	13 (10)	78 (63)	83 (67)
% Employed***					
<60%	345 (31)	146 (42)	38 (11)	161 (47)	184 (53)
60% - 71%	396 (35)	197 (50)	34 (9)	165 (42)	186 (47)
≥71%	375 (34)	229 (61)	31 (8)	115 (31)	168 (45)
Median annual household income***					
(Q1) <38,885	301 (28)	122 (41)	28 (9)	151 (50)	168 (56)
(Q2) 38,885-51,004	272 (24)	141 (52)	26 (10)	105 (39)	141 (52)
(Q3) 51,004-66,774	272 (24)	134 (49)	20 (7)	118 (43)	127 (47)
(Q4) 66,774 or more	271 (24)	175 (65)	29 (11)	67 (25)	102 (38)

Table 2.1: Characteristics of Patients with Stage III Colon Cancer in Alberta with Respect to Receiving Adjuvant Chemotherapy and their Mortality (continued)

Patients, Characteristics	Total N (%[1])	Time to Adjuvant Chemotherapy N (%[2])			Patients who died N (%[2])
		≤ 12 Weeks	> 12 weeks	No treatment	
Total	**1116 (100)**	**572 (51)**	**103 (9)**	**441 (40)**	**538 (48)**
% Not graduated from high school**					
< 27% (median)	575 (52)	319 (55)	55 (10)	201 (35)	262 (46)
≥ 27% (median)	541 (48)	253 (47)	48 (9)	240 (44)	276 (51)
No. of co-morbidities***					
0	643 (65)	394 (61)	50 (8)	199 (31)	280 (44)
1	198 (20)	82 (41)	17 (9)	99 (50)	110 (56)
2 or more	148 (15)	19 (13)	14 (9)	115 (78)	103 (70)
Year of Diagnosis					
2000	170 (15)	93 (55)	20 (12)	57 (34)	91 (54)
2001	175 (16)	92 (53)	18 (10)	65 (37)	92 (53)
2002	179 (16)	97 (54)	15 (8)	67 (37)	94 (53)
2003	208 (19)	101 (49)	24 (12)	83 (40)	108 (52)
2004	197 (17)	91 (46)	11 (6)	95 (48)	85 (43)
2005	187 (17)	98 (52)	15 (8)	74 (40)	68 (36)

Note: ***P<0.001; **P<0.01; *P<0.05 P-values are based on tests of equality across the three "Time to Adjuvant Chemotherapy" intervals and the categories of the corresponding variable,
1 - Column percent
2 - Row percent

Table 2.2: Adjusted[1] Overall and Colon Cancer-Specific Mortality Hazard Ratios for Patients with Stage III Colon Cancer

Covariates	Overall Mortality[2]			Colon Cancer Mortality[2]		
	HR[3]	95% CI	P-value	HR[2]	95% CI	P-value
Time to chemotherapy			**<0.001**			**<0.001**
< 8 weeks	**ref**			**ref**		
8–12 weeks	0.97	0.71-1.34	0.87	0.89	0.63-1.25	0.50
12-16 weeks	1.68	1.12-2.51	0.01	1.32	0.83-2.09	0.24
> 16 weeks or no treatment	2.17	1.62-2.91	<0.001	1.84	1.33-2.55	<0.001
Sex			**0.72**			**0.97**
Male	**ref**			**ref**		
Female	1.04	0.86-1.25	0.72	1.00	0.80-1.24	0.97
Residence at diagnosis			**0.05**			**0.06**
Edmonton & area	**ref**			**ref**		
South	1.50	1.09-2.07	0.01	1.45	0.99-2.12	0.06
Calgary & area	1.24	0.97-1.58	0.08	1.26	0.94-1.68	0.12
Central	1.44	1.08-1.90	0.01	1.60	1.16-2.20	0.004
North	1.32	0.93-1.85	0.12	1.28	0.86-1.89	0.23
% Divorced, separated or widowed			**0.07**			**0.19**
<13% d/s/w	**ref**			**ref**		
13% - 29% d/s/w	0.97	0.74-1.26	0.81	1.08	0.79-1.48	0.61
≥29% d/s/w	1.41	0.96-2.07	0.08	1.48	0.94-2.33	0.09
% Employed			**0.42**			**0.86**
<60%	0.91	0.69-1.20	0.49	0.95	0.69-1.32	0.77
60% - 71%	0.85	0.66-1.09	0.19	0.92	0.69-1.24	0.60
≥71%	**ref**			**ref**		
Median annual household income			**0.29**			**0.14**
(Q1) <38,885	1.16	0.80-1.69	0.43	1.10	0.71-1.70	0.66
(Q2) 38,885-51,004	1.36	0.95-1.94	0.09	1.34	0.89-2.02	0.16
(Q3) 51,004-66,774	1.11	0.80-1.54	0.53	0.94	0.63-1.38	0.73
(Q4) 66,774 or more	**ref**			**ref**		
No. of co-morbidities			**0.14**			**0.77**
0	**ref**			**ref**		
1	1.01	0.80-1.28	0.92	0.97	0.73-1.28	0.82
2 or more	1.29	1.00-1.68	0.06	1.11	0.8-1.53	0.55

Table 2.2: Adjusted[1] Overall and Colon Cancer-Specific Mortality Hazard Ratios for Patients with Stage III Colon Cancer (continued)

Covariates	Overall Mortality[2]			Colon Cancer Mortality[2]		
	HR[3]	95% CI	P-value	HR[2]	95% CI	P-value
Year of Diagnosis			**0.03**			**0.004**
2000	**ref**			**ref**		
2001	1.13	0.81-1.57	0.48	1.30	0.89-1.89	0.18
2002	1.25	0.89-1.76	0.2	1.28	0.86-1.91	0.23
2003	1.68	1.19-2.36	0.003	1.94	1.30-2.89	0.001
2004	1.32	0.91-1.93	0.15	1.52	0.96-2.39	0.07
2005	1.67	1.13-2.47	0.01	2.31	1.45-3.70	0.001

Note: 1 - Adjusted for age at diagnosis using a natural cubic spline with 4 knots
2 - Survival time starts at 16 weeks after surgery
3 - Adjusted Hazard Ratios

2.5 References

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Chapter 3: Timing of Adjuvant Treatment and Survival in Patients with Stage II/III Rectal Cancer

3.1 Introduction

The National Institute of Health (NIH) Consensus Conference in 1990 established surgical resection of adenocarcinoma of the rectum followed by adjuvant chemo-radiotherapy (post-operative chemotherapy and radiotherapy) as the recommended treatment for patients diagnosed with stage II or III disease (1). This guideline was based on the results of several large randomized controlled trials (2-4) and became the standard of care for patients with stage II/III rectal cancer in the United States. More recent studies have shown that neoadjuvant chemoradiotherapy (pre-operative chemotherapy and radiotherapy) significantly reduces local recurrence rates (5-9) and improves disease-free survival among stage II/III rectal cancer patients (9, 10). The majority of the patients in the clinical trials initiated adjuvant treatment within 6 weeks after surgery; this may not be easy to achieve in practice due to post-operative complications and/or healthcare system limitations. The optimum timing for adjuvant treatment initiation for surgically resected stage II/III rectal patients, therefore, remains unclear.

In Alberta, Canada, the recommendation for patients diagnosed with stage II/III rectal adenocarcinoma is neoadjuvant radiation with or without chemotherapy and/or adjuvant chemotherapy with or without radiation. Adjuvant treatment should be initiated within twelve weeks of surgery.

The goals of this study are to: 1) describe treatment patterns of patients diagnosed with stage II/III rectal cancer between 2000 and 2005; 2) estimate the proportion of patients receiving adjuvant treatment within 12 weeks after surgery; 3) identify patient/clinical characteristics associated with receipt of adjuvant treatment within 12 weeks after surgery; and 4) determine whether there is a relationship between the timing of adjuvant treatment and survival of patients diagnosed with stage II/III rectal cancer.

3.2 Methods

3.2.1 Study Population

The province of Alberta has approximately 3 million residents; about two-thirds live in Edmonton or Calgary, the two largest cities. The province provides a universal and publicly-funded health care system for its residents. Standard cancer treatments are free to patients as are associated visits to cancer facilities, including consultations with oncologists. Physicians and hospitals are legally required to report every cancer case they diagnose to the Alberta Cancer Registry, a member of the North American Association of Comprehensive Cancer Registries. The Alberta Cancer Registry, established in 1942, is routinely recognized for the high quality of its data (11).

All residents of Alberta who were diagnosed in 2000 to 2005 with stage II or III rectal adenocarcinoma (International Classification of Diseases for Oncology (ICD-O) (12) code c19 and C20) were identified from the Alberta

Cancer Registry. Patients were excluded if they did not receive surgery, died within one week of their diagnosis, were diagnosed with another primary cancer 6 months prior or subsequent to their rectal cancer diagnosis, did not have histologically confirmed adenocarcinoma, or were treated outside of Alberta. Cancer staging was based on the TNM (Tumor, Node, and Metastasis) system from the American Joint Committee on Cancer (AJCC version 6) (13). Local invasive tumors (T3-4) that have not spread to regional lymph nodes (N0) or distant metastatic sites (M0) were defined as stage II. Invasive tumors of any size (T1-4) that have spread to at least one regional lymph node (N1-3) but not to distant metastatic sites (M0) were defined as stage III.

3.2.2 Data Sources

Data were linked from four different data sources: Alberta Cancer Registry (the primary data source for the study), Ambulatory Care Classification System (ACCS), Discharge Abstract Database (DAD), and the 2001 Canadian census. The Alberta Cancer Registry is responsible for recording and maintaining data on all cancer cases and cancer deaths occurring in Alberta. Patient demographics, tumor histology and stage, postal code of residence at diagnosis, initial treatment modalities and start dates, and date of death, if deceased, were obtained from the Alberta Cancer Registry.

The ACCS and DAD databases contain diagnosis and procedure codes on all outpatient and inpatient hospital visits, respectively, in the province of Alberta. All hospital visits that occurred in the year prior to the patient's cancer diagnosis

were used to identify co-morbidities using an enhancement (14) to the Charlson Co-morbidity Index (15). Co-morbidity scores were categorized into three groups: no serious co-morbidity; one serious co-morbidity; and two or more serious co-morbidities.

The 2001 Canadian census was used to obtain socioeconomic indicators at the neighborhood level (census dissemination areas) for each patient. Four variables were used as measures of neighborhood socioeconomic status: 1) median income; 2) proportion of employment; 3) proportion separated, divorced, or widowed; and 4) proportion not graduated from high school.

3.2.3 Statistical Analysis

Descriptive statistics were calculated and Chi-square or Fisher's Exact tests, as appropriate, were used to assess associations between patient/clinical characteristics and treatment regimen received. Patient and clinical characteristics evaluated include: time to adjuvant treatment; stage; gender; age at diagnosis; region of residence at diagnosis; neighborhood socioeconomic status; number of co-morbidities; and year of diagnosis. Treatment was defined as: "Surgery only" if curative surgery was the only treatment received; "Neoadjuvant treatment only" if radiotherapy with or without chemotherapy was administered prior to surgery, without any post-operative treatment; "Adjuvant treatment only" if post-operative treatment (chemotherapy, radiotherapy, or both) was given without any pre-operative treatment; and "Neo + adjuvant treatment" if both neoadjuvant and adjuvant treatment were received.

Time from the date of surgery to the date of first adjuvant treatment session (radiotherapy followed by chemotherapy or chemotherapy, whichever occurred first) was calculated and patients were categorized into the following four groups for statistical analysis: received adjuvant treatment within 8 weeks after surgery; 8-12 weeks after surgery; greater than 12 weeks; or did not received recommended adjuvant treatment. Exploratory data analysis was performed to determine these cut-offs. The final categories were used to evaluate the effect of the timing of adjuvant treatment initiation on patient survival, including those who did not receive recommended adjuvant treatment.

Kaplan-Meier curves were used to describe patient survival stratified by time from surgery to adjuvant treatment. Cumulative incidence curves were used to describe the cumulative mortality due to rectal cancer-specific deaths, treating the other causes of death as competing risk (16). The Kaplan-Meier and cumulative incidence curves were started at 12 weeks after surgery. Deaths prior to this starting time were not included in the analysis; this is to alleviate immortal bias due to the time dependence in the definition of the groups for timing of adjuvant treatment initiation: those who start adjuvant treatment at X weeks from surgery must survive X weeks to receive the therapy and are by definition immortal during this period.

Cox proportional hazards models were used to estimate the adjusted hazard ratios (HRs) of overall and cancer-specific mortality by time from surgery to adjuvant treatment (time dependent covariate), starting at 12 weeks after

surgery. The following covariates were included in the Cox regression models to estimate adjusted HRs: stage; neoadjuvant treatment status; gender; age at diagnosis; region of residence at diagnosis; number of co-morbidities; year of diagnosis; and neighborhood-level socioeconomic factors. Two-way interactions, hypothesized *a priori*, between time to adjuvant treatment, stage, and neoadjuvant treatment status were tested in the model, separately one at a time. In order to closely adjust for age at diagnosis, a natural cubic spline of age at diagnosis was used with four knots (17). Patients were followed to the first event of death or March 31, 2009.

Patients who died soon after surgery and did not have an opportunity to receive adjuvant treatment were included in the group "did not receive adjuvant treatment" which may improperly increase the HR of death in this group. A sensitivity analysis was, therefore, conducted to assess whether changing the start time (T0) would result in different HR estimates for the timing of adjuvant treatment on survival. Two different time points for T0 were considered in the sensitivity analysis: date of surgery and 12 weeks post-surgery. Both analyses provided similar results, therefore, T0=12 weeks after surgery was used to protect against the time dependence bias resultant from the time to adjuvant treatment categorization.

All statistical analyses were conducted using SAS statistical software version 9.2 (SAS Institute, Cary, NC, USA) and R version 2.9 (R Foundation for Statistical Computing, Vienna, Austria).

3.3 Results

There were 1,394 residents of Alberta diagnosed with stage II or III rectal cancer in the years 2000 to 2005. The following number of patients were excluded from the study based on the exclusion criteria described above: 40 patients did not have surgery; 6 patients died within one week of their diagnosis; 48 patients were diagnosed with another cancer within six months prior or subsequent to their rectal cancer diagnosis; 14 patients did not have histological confirmation of their disease; 6 patients had a histology other than adenocarcinoma; and 1 patient was treated outside of Alberta. The remaining 1,279 patients were included in the study.

Table 3.1 shows the baseline characteristics of the 1,279 patients included in the study stratified by type of treatment received. Overall, 460 (36%) of the stage II/III rectal cancer patients did not receive any pre- or post-operative treatment, 138 (11%) received neoadjuvant treatment only, 546 (43%) received adjuvant treatment only, and 135 (10%) patients received both neoadjuvant and adjuvant treatment.

Treatment differed by stage ($P<0.001$); 45% of patients diagnosed with stage II rectal cancer received only surgery and 29% received adjuvant treatment only. Conversely, 27% of the patients with stage III rectal cancer received surgery only and 56% received adjuvant treatment only. Higher co-morbidity scores, older age, and living in lower socioeconomic neighborhoods were each associated with lower rates of both pre- and post-surgical treatment (Table 3.1). The proportion of patients treated by surgery alone decreased significantly over time

with a proportional increase over time in those who received both neoadjuvant and adjuvant treatment.

Table 3.2 shows the demographic, clinical, and neighborhood-level socioeconomic characteristics of patients stratified by time from surgery to the receipt of adjuvant treatment. Stage II rectal cancer patients, those aged 75 years and older, and those with two or more severe co-morbidities were least likely to receive adjuvant treatment or receive it within 12 weeks of surgery. Lower rates of adjuvant treatment were also seen among those who live in neighborhoods with a high percentage of divorced, separated or widowed, a low employment rate, and a low median household income.

Figures 3.1 and 3.2 show the Kaplan-Meier and cumulative incidence curves for the overall survival and rectal cancer-specific mortality, respectively, by time from surgery to adjuvant treatment. The rectal cancer-specific mortality appears to be grouped into two groups: 1) those who did not receive adjuvant treatment or received it 12 weeks or more after surgery, and 2) those who received it within 12 weeks. Those who received adjuvant treatment within 12 weeks of their surgery had a significantly lower rectal cancer-specific mortality than those who did not receive it.

Table 3.3 presents the fit of the Cox proportional hazards models. None of the interaction terms tested were significant so only the main effects model is shown. The adjusted mortality HRs and corresponding 95% confidence intervals (overall and rectal cancer-specific) for patients with stage II/III rectal cancer were adjusted for all variables shown in the table. There was no difference in the

overall or rectal cancer-specific mortality hazard for patients who received adjuvant treatment 8-12 weeks after surgery relative to those who received it within 8 weeks. The rectal cancer-specific HR for patients who received adjuvant treatment 12 weeks or more after surgery, compared to those who received it within 8 weeks after surgery, was 1.40 (95% confidence interval (CI) 0.89-2.21). This estimate was similar to the HR for those who did not receive adjuvant treatment, 1.60 (95%CI 1.11-2.31). Patients who did not receive adjuvant treatment also had a 1.72 times higher overall mortality hazard compared to those who received the treatment within 8 weeks after surgery (HR=1.72, 95%CI 1.26-2.37).

3.4 Discussion

The primary aim of this study was to determine whether there was a relationship between the timing of initiation of adjuvant treatment and survival for patients diagnosed with stage II/III rectal cancer. Additionally, we aimed to quantify the proportion of patients who received adjuvant treatment within 12 weeks after surgery and their association with patient/clinical characteristics.

Of those diagnosed with stage II/III rectal cancer in Alberta between 2000 and 2005 and who met the inclusion criteria, 556 (43%) patients received adjuvant treatment within 12 weeks after surgery. The remaining patients, however, either received delayed adjuvant treatment (10%) or did not receive it at all (47%). Over one-third of them (36%) received surgery alone as their treatment. Factors strongly associated with not receiving adjuvant treatment were:

75 years or older; diagnosed with stage II disease; presence of one or more serious co-morbidities; living in neighborhoods with low socio-economic indicators; and region of residence. Both clinical trials and population-based studies have shown that elderly patients and those with co-morbidities can benefit from pre-operative (6, 9-10) and post-operative (8, 18-22) therapy. Older age and co-morbidities may be related to post-surgical complications or delayed recovery that could affect whether a patient received adjuvant treatment and/or the timing of it; we were not able to evaluate these possibilities in our study.

In a publicly-funded healthcare system, however, factors such as region of residence and socioeconomic status should not be related to the receipt of standard treatment, as we found in the study described herein. Similar results have also been found in patients with stage III colon cancer diagnosed in Alberta (23). Collectively, these results suggest that provision of free healthcare services does not, in and of itself, eliminate access barriers to standard care. Research is needed to improve understanding of barriers related to region/neighborhood of residence and socioeconomic status.

Few studies have compared standard treatment rates by disease stage for rectal cancer, but those that have also found lower adherence among patients with stage II disease relative to those with stage III disease (24). Reasons for this are not clear, although it may be due, at least in part, to failure to refer patients to an oncologist. This is supported by a recent finding (manuscript submitted) that residents of Alberta diagnosed with stage II rectal cancer were less likely to have a consultation with an oncologist than those with stage III disease, a prerequisite

to receiving radiation and/or chemotherapy in Alberta. Surgeons and/or family physicians may not be aware of the difference in standard treatment for stage II rectal cancer versus stage II colon cancer. Alternatively, they may think that only tumors that have spread to lymph nodes (i.e., stage III) warrant adjuvant treatment. Regardless, efforts are needed to increase the proportion of patients with stage II rectal cancer who receive adjuvant treatment in order to improve survival and maximize patient outcomes.

Additionally, further investigation to identify the reasons for receiving delayed treatment is needed to optimize patient outcomes. Physicians may delay radiation and/or chemotherapy due to a slow recovery from surgery, post-surgery complications, or possibly a change in the patient's decision to receive adjuvant therapy. Alternatively, delays may occur due to inefficiencies in the health care system or to shortages of resources to deliver care.

This is the first population-based study conducted in North America to investigate the association between timing of adjuvant treatment initiation and survival among patients with stage II/III rectal cancer. Current treatment guidelines in Alberta are supported by this study: patients with stage II/III rectal cancer should receive adjuvant treatment within 12 weeks of surgery. Patients who received adjuvant treatment more than 12 weeks post-surgery or not at all, were 1.40 and 1.60 times, respectively, more likely to die of rectal cancer than those who received treatment within 8 weeks of surgery, after adjusting for relevant factors. Although the HR for the group who received adjuvant treatment more than 12 weeks after surgery was only marginally statistically significant (P=

0.15), it is a clinically significant increase and is consistent with the HR for the "no adjuvant treatment" group. Furthermore, the rectal cancer-specific cumulative incidence curves for the two groups are similar to each other and distinct from the curves for the patients that were treated within 8 weeks or treated within 8 to 12 weeks of surgery. The statistical significance of this result was influenced by the relatively small number of patients who received adjuvant treatment more than 12 weeks post-surgery (125 patients).

The finding that 12 weeks is the maximum time that should elapse from surgery to initiation of adjuvant treatment is consistent with findings from a study we conducted on patients with stage III colon cancer (manuscript submitted) as well as another study conducted with stage III colon cancer patients using the US National Cancer Institute's Surveillance, Epidemiology, and End Results data (25). All three studies found that patients should receive adjuvant treatment within 12 weeks of surgery to maximize patient survival. The consistency of these findings across different study populations, despite slightly different study methodologies, and across colon and rectal cancers is significant.

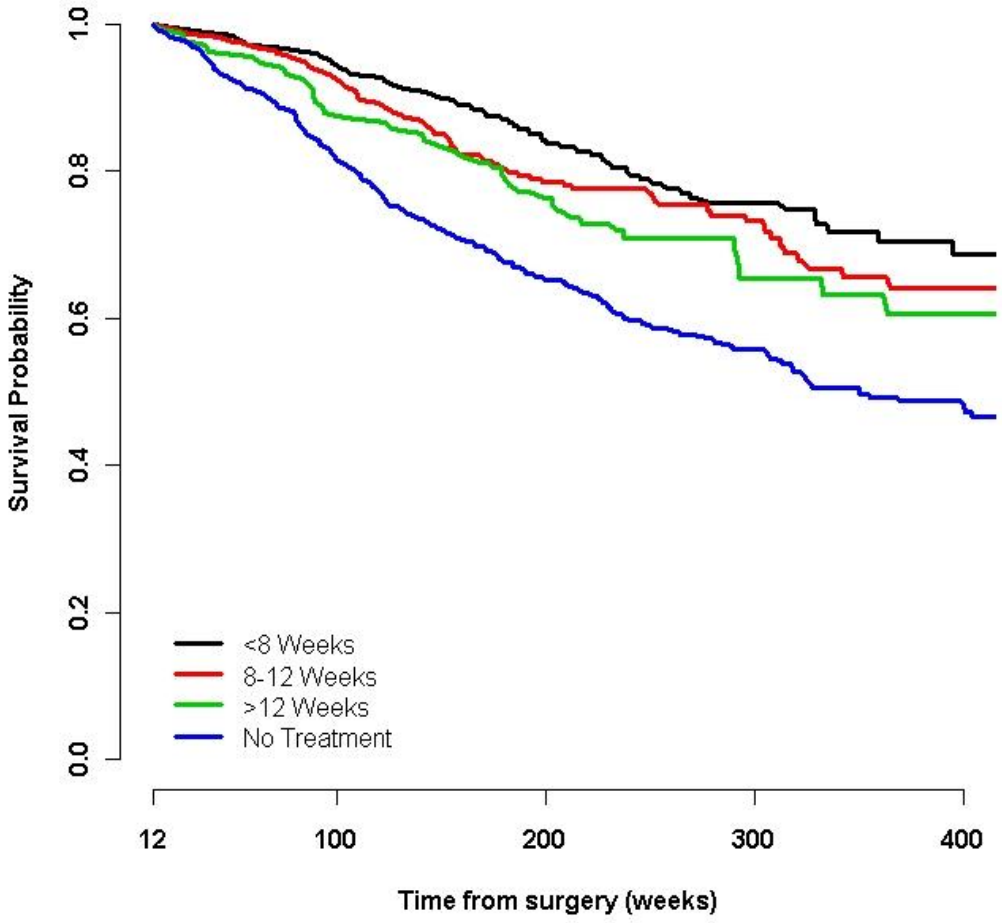
A surprising result was that patients who received neoadjuvant treatment had a significantly higher risk of both overall and rectal cancer-specific death than those who did not receive neoadjuvant treatment (HR=1.38, 95%CI 1.05-1.81, p=0.02 and HR=1.56, 95%CI 1.13-2.14, p=0.006, respectively). These results should be interpreted with caution. A probable explanation is that patients who received neoadjuvant treatment were different in clinically-relevant ways than those who did not receive it. Neoadjuvant treatment is given specifically to shrink

tumors that are large and/or suspected of increasing the risk of local recurrence. Clinical trials have found neoadjuvant radiation and/or combined chemoradiation to be effective in doing so (9,10), but no comparisons have been made between patients who are clinically determined to not need neoadjuvant treatment and those who are clinically determined to need neoadjuvant treatment with respect to their risk of death. Our findings suggest that even though the risk of local recurrence is decreased amongst those who need and receive neoadjuvant treatment (based on clinical trials), their risk of rectal cancer-specific death is still higher than those patients who do not clinically require neoadjuvant treatment.

The findings of this study are robust and generalizable. Our linked dataset is a powerful tool and includes all patients diagnosed in the province of Alberta over a six-year period with up to nine years of follow-up. Limitations of the study, however, are that we did not have treatment details, such as completeness of the regimen or the specific treatment regimens received. Also, we did not have access to other important factors that could have an effect on patient survival, such as surgical complications and patient's functional status. This limitation was addressed to some extent, however, by starting the survival time at 12 weeks post-surgery in the survival analysis. This approach prevented potential over-estimation of HRs for those who never received adjuvant treatment by excluding those who died soon after surgery. These patients probably did not have the opportunity to receive adjuvant therapy due to poor health post-surgery and probably would not have benefited from it. Thus, our HR estimates are conservative.

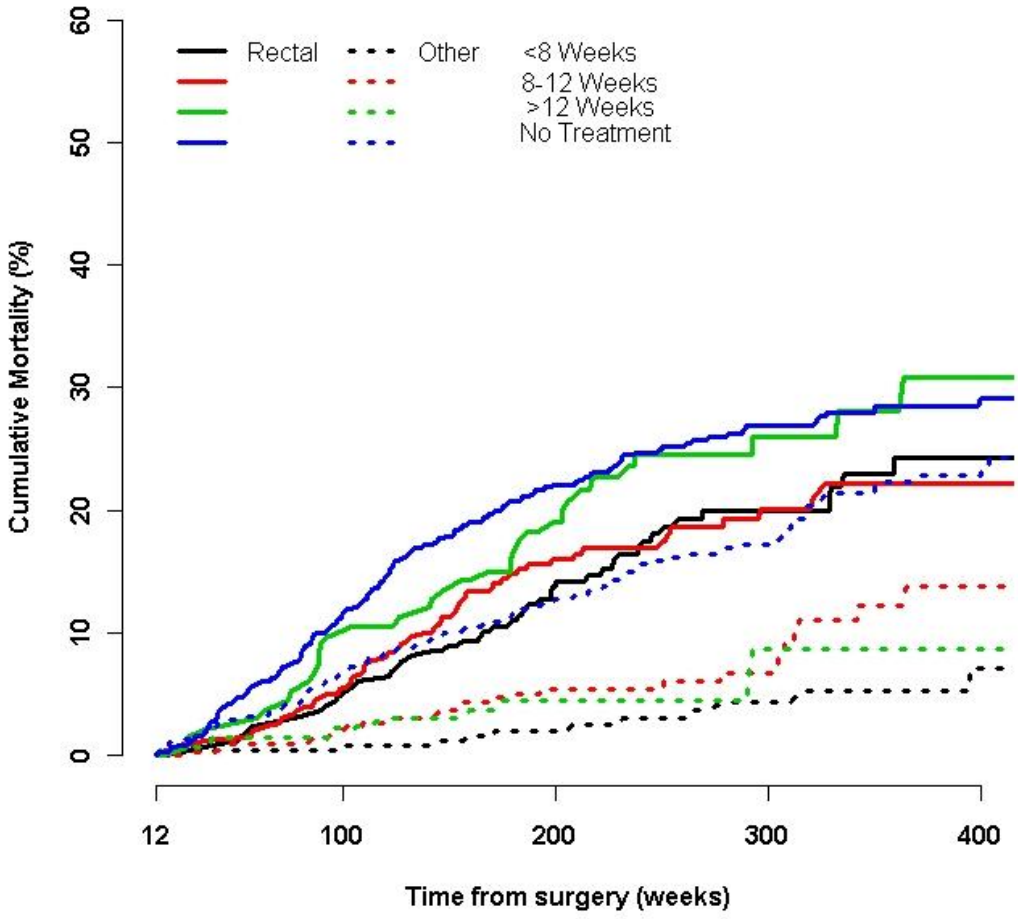
In summary, we found that 47% of patients diagnosed with stage II/III rectal cancer between 2000 and 2005 in Alberta, Canada, did not receive adjuvant treatment, and 10% received it more than 12 weeks after surgery. Patients who received treatment more than 12 weeks post-surgery or did not receive it were more likely to die compared to those who received adjuvant treatment within 8 weeks after surgery. Interventions are needed to ensure timely receipt of adjuvant treatment for patients with stage II/III rectal cancer in order to optimize patient outcomes.

Figure 3.1: Kaplan-Meier Curves for the Overall Survival of Stage II/III Rectal Cancer Patients by Time from Surgery to Adjuvant Treatment.



Note: Time from surgery to adjuvant treatment starts at 12 weeks after surgery.

Figure 3.2: Cumulative Incidence Curves for Rectal Cancer-Specific Mortality by Time from Surgery to Adjuvant Treatment.



Note: Time from surgery to adjuvant treatment starts at 12 weeks after surgery.

Table 3.1: Characteristics of Patients with Stage II/III Rectal Cancer in Alberta with Respect to Treatments Received

Patients' Characteristics	Total N (%[1])	Treatments N (%[2]) Surgery only	Neoadjuvant treatment only	Adjuvant treatment only	Neo + adjuvant Treatment[£]
Total	**1,279 (100)**	**460 (36)**	**138 (11)**	**546 (43)**	**135 (10)**
Time to Adjuvant treatment***					
<8 weeks	248 (20)	0 (0)	0 (0)	194 (78)	54 (22)
8-12 weeks	300 (23)	0 (0)	0 (0)	240 (80)	60 (20)
≥12 Weeks	133 (10)	0 (0)	0 (0)	112 (84)	21 (16)
No adjuvant treatment	598 (47)	460 (77)	138 (23)	0 (0)	0 (0)
Stage***					
II	633 (49)	287 (45)	91 (14)	186 (29)	69 (11)
III	646 (51)	173 (27)	47 (7)	360 (56)	66 (10)
Sex**					
Female	483 (38)	199 (41)	37 (8)	204 (42)	43 (9)
Male	796 (62)	261 (33)	101 (13)	342 (43)	92 (12)
Age at diagnosis***					
<65 years	518 (40)	66 (13)	75 (14)	286 (55)	91 (18)
65 - 75 years	383 (30)	125 (33)	36 (9)	191 (50)	31 (8)
≥75 years	378 (30)	269 (71)	27 (7)	69 (18)	13 (3)
Residence at diagnosis**					
South	113 (9)	48 (42)	6 (5)	49 (43)	10 (9)
Calgary & area	421 (33)	141 (33)	40 (10)	199 (47)	41 (10)
Central	201 (15)	91 (45)	17 (8)	79 (39)	14 (7)
Edmonton & area	406 (32)	137 (34)	58 (14)	159 (39)	52 (13)
North	138 (11)	43 (31)	17 (12)	60 (43)	18 (13)
%Divorced, separated or widowed***					
<13% d/s/w	430 (34)	120 (28)	55 (13)	205 (48)	50 (12)
13% - 29% d/s/w	734 (57)	277 (38)	73 (10)	308 (42)	76 (10)
≥29% d/s/w	115 (9)	63 (55)	10 (9)	33 (29)	9 (8)

Table 3.1: Characteristics of Patients with Stage II/III Rectal Cancer in Alberta with Respect to Treatments Received (continued)

Patients, Characteristics	Total N (%[1])	Treatments N (%[2]) Surgery only	Neoadjuvant treatment only	Adjuvant treatment only	Neo + adjuvant Treatment[£]
% Employed* **					
<60%	405 (31)	177 (44)	42 (10)	148 (37)	38 (9)
60% - 71%	443 (35)	167 (38)	48 (11)	181 (41)	47 (11)
≥71%	431 (34)	116 (27)	48 (11)	217 (50)	50 (12)
Median annual household income* **					
(Q1) <38,885	340 (27)	151 (44)	37 (11)	115 (34)	37 (11)
(Q2) 38,885-51,004	329 (26)	118 (36)	40 (12)	143 (43)	28 (9)
(Q3) 51,004-66,774	326 (25)	121 (37)	29 (9)	142 (44)	34 (10)
(Q4) 66,774 or more	285 (22)	70 (25)	33 (12)	146 (51)	36 (13)
% Not graduated from high school* **					
< 27% (median)	640 (50)	194 (30)	72 (11)	302 (47)	72 (11)
≥27% (median)	639 (50)	266 (42)	66 (10)	244 (38)	63 (10)
No. of co-morbidities* **					
0	1059 (83)	327 (31)	117 (11)	484 (46)	131 (12)
1	144 (11)	82 (57)	14 (10)	46 (32)	2 (1)
2 or more	76 (6)	51 (67)	7 (9)	16 (21)	2 (3)
Year of diagnosis* **					
2000	184 (14)	79 (43)	15 (8)	79 (43)	11 (6)
2001	188 (15)	75 (40)	29 (15)	78 (41)	6 (3)
2002	198 (16)	75 (38)	9 (5)	95 (48)	19 (10)
2003	217 (17)	82 (38)	18 (8)	101 (47)	16 (7)
2004	234 (18)	80 (34)	34 (15)	91 (39)	29 (12)
2005	258 (20)	69 (27)	33 (13)	102 (40)	54 (21)

Note: ***P<0.001; **P<0.01; *P<0.05 P-values are based on tests of equality across the four "Treatment" intervals and the categories of the corresponding variable

1 - Column percent

2 - Row percent

Table 3.2: Characteristics of Patients with Stage II/III Rectal Cancer in Alberta with Respect to Receiving Guideline Adjuvant Treatment

Patients' Characteristics	Total	Time to Adjuvant Treatment N (%[2])		
	N (%[1])	≤12 Weeks	> 12 Weeks	No adjuvant treatment
Total	**1,279 (100)**	**556 (43)**	**125 (10)**	**598 (47)**
Stage* **				
II	633 (49)	200 (32)	55 (8)	378 (60)
III	646 (51)	356 (55)	70 (11)	220 (34)
Sex*				
Female	483 (38)	194 (40)	53 (11)	236 (49)
Male	796 (62)	362 (45)	72 (9)	362 (46)
Age at diagnosis* **				
<65 years	518 (40)	328 (63)	49 (10)	141 (27)
65 - 75 years	383 (30)	173 (45)	49 (13)	161 (42)
≥75 years	378 (30)	55 (15)	27 (7)	296 (78)
Residence at diagnosis* **				
South	113 (9)	50 (44)	9 (8)	54 (48)
Calgary & area	421 (33)	179 (42)	61 (15)	181 (43)
Central	201 (15)	68 (34)	25 (12)	108 (54)
Edmonton & area	406 (32)	192 (47)	19 (5)	195 (48)
North	138 (11)	67 (49)	11 (8)	60 (43)
%Divorced, separated or widowed* **				
<13% d/s/w	430 (34)	201 (47)	54 (13)	175 (40)
13% - 29% d/s/w	734 (57)	321 (44)	63 (9)	350 (48)
≥29% d/s/w	115 (9)	34 (30)	8 (7)	73 (63)
% Employed* **				
<60%	405 (31)	144 (36)	42 (10)	219 (54)
60% - 71%	443 (35)	190 (43)	38 (9)	215 (49)
≥71%	431 (34)	222 (51)	45 (10)	164 (39)

Table 3.2: Characteristics of Patients with Stage II/III Rectal Cancer in Alberta with Respect to Receiving Guideline Adjuvant Treatment (continued)

Patients Characteristics	Total	Time to Adjuvant Treatment N (%[2])		
	N (%[1])	≤12 Weeks	> 12 Weeks	No adjuvant treatment
Median annual household income* **				
(Q1) <38,885	340 (27)	123 (36)	29 (9)	188 (55)
(Q2) 38,885-51,004	329 (26)	140 (43)	31 (9)	158 (48)
(Q3) 51,004-66,774	326 (25)	146 (45)	30 (9)	150 (46)
(Q4) 66,774 or more	285 (22)	147 (52)	35 (12)	102 (36)
% Not graduated from high school* **				
< 27% (median)	640 (50)	298 (46)	76 (12)	266 (42)
≥27% (median)	639 (50)	258 (40)	49 (8)	332 (52)
No. of co-morbidities* **				
0	1059 (83)	504 (48)	111 (10)	444 (42)
1	144 (11)	41 (28)	7 (5)	96 (67)
2 or more	76 (6)	11 (14)	7 (9)	58 (76)
Year of diagnosis*				
2000	184 (14)	74 (40)	16 (9)	94 (51)
2001	188 (15)	66 (35)	18 (10)	104 (55)
2002	198 (16)	89 (45)	25 (13)	84 (42)
2003	217 (17)	97 (45)	20 (9)	100 (46)
2004	234 (18)	95 (40)	25 (11)	114 (49)
2005	258 (20)	135 (52)	21 (8)	102 (40)

Note: ***P<0.001; **P<0.01; *P<0.05 P-values are based on tests of equality across the three "Time to Adjuvant Treatment" intervals and the categories of the corresponding variable
1 - Column percent
2 - Row percent

Table 3.3: Adjusted[1] Overall and Rectal Cancer-Specific Mortality Hazard Ratios for Patients with Stage II/III Rectal Cancer

	Overall Mortality[2]			Rectum Cancer Mortality[2]		
Covariates	**HR[3]**	**95% CI**	**P-value**	**HR[3]**	**95% CI**	**P-value**
Time to adjuvant treatment			**0.005**			**0.03**
< 8 weeks	**ref**			**ref**		
8–12 weeks	1.25	0.89-1.76	0.20	1.04	0.70-1.54	0.84
≥12 weeks	1.37	0.91-2.06	0.13	1.40	0.89-2.21	0.15
No adjuvant treatment	1.72	1.26-2.37	0.001	1.60	1.11-2.31	0.01
Neoadjuvant treatment			**0.02**			**0.006**
No	**ref**			**ref**		
Yes	1.38	1.05-1.81	0.02	1.56	1.13-2.14	0.006
Stage			**<0.001**			**<0.001**
II	**ref**			**ref**		
III	2.13	1.74-2.60	<0.001	2.50	1.94-3.23	<0.001
Sex			**0.001**			**0.70**
Male	**ref**			**ref**		
Female	0.71	0.58-0.87	0.001	0.95	0.75-1.22	0.70
Residence at diagnosis			**0.51**			**0.09**
Edmonton & area	**ref**			**ref**		
South	1.12	0.78-1.60	0.54	1.60	1.04-2.46	0.03
Calgary & area	0.95	0.74-1.22	0.70	1.23	0.89-1.70	0.21
Central	1.19	0.89-1.58	0.25	1.56	1.08-2.25	0.02
North	1.23	0.88-1.73	0.22	1.49	0.98-2.27	0.06
% Divorced, separated or widowed			**0.54**			**0.29**
<13% d/s/w	**ref**			**ref**		
13% - 29% d/s/w	1.12	0.85-1.46	0.43	1.17	0.85-1.63	0.34
≥29% d/s/w	0.96	0.63-1.46	0.85	0.85	0.49-1.47	0.56
% Employed			**0.76**			**0.39**
<60%	0.95	0.73-1.26	0.74	0.99	0.70-1.39	0.93
60% - 71%	1.04	0.81-1.33	0.75	1.17	0.87-1.59	0.30
≥71%	**ref**			**ref**		

Table 3.3: Adjusted[1] Overall and Rectal Cancer-Specific Mortality Hazard Ratios for Patients with Stage II/III Rectal Cancer (continued)

	Overall Mortality[2]			Rectum Cancer Mortality[2]		
Covariates	**HR[3]**	**95% CI**	**P-value**	**HR[3]**	**95% CI**	**P-value**
Median annual household income			**0.35**			**0.42**
(Q1) <38,885	1.19	0.81-1.75	0.37	1.27	0.79-2.05	0.32
(Q2) 38,885-51,004	1.19	0.82-1.71	0.36	1.30	0.82-2.04	0.26
(Q3) 51,004-66,774	0.95	0.67-1.33	0.75	1.00	0.66-1.53	0.99
(Q4) 66,774 or more	**ref**			**ref**		
No. of co-morbidities			**<0.001**			**0.30**
0	**ref**			**ref**		
1	1.30	0.99-1.70	0.06	1.21	0.85-1.73	0.29
2 or more	1.85	1.33-2.57	<0.001	1.37	0.85-2.21	0.20
Year of diagnosis			**0.22**			**0.98**
2000	**ref**			**ref**		
2001	0.80	0.58-1.09	0.15	0.93	0.62-1.38	0.70
2002	0.78	0.56-1.07	0.13	0.89	0.59-1.34	0.57
2003	0.69	0.49-0.97	0.03	0.88	0.57-1.36	0.56
2004	0.77	0.54-1.08	0.13	0.99	0.64-1.53	0.96
2005	0.63	0.43-0.92	0.018	0.92	0.57-1.49	0.73

Note: 1 - Adjusted for all variables shown in the table, age at diagnosis using a cubic spline with 4 knots and % of graduated from high school in the neighborhood
2 - Survival time starts at 12 weeks after surgery
3 - Adjusted Hazard Ratios

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Chapter 4: Discussion and Conclusions

4.1 Review of Hypotheses

Hypothesis 1 (Chapter 2)

- Those who have received adjuvant chemotherapy 8-12 weeks after surgery will have similar survival probabilities as patients who received it within 8 weeks.
  - ***We found evidence in our data to support this hypothesis. Starting adjuvant chemotherapy in 8-12 weeks after surgery, instead of within 8 weeks, does not appear to alter patient survival appreciably.***
- Patients who have received adjuvant chemotherapy 12-16 weeks after their surgery will be associated with higher hazard of both overall and colon cancer-specific mortality, compared to patients who initiated adjuvant chemotherapy within 8 weeks after their surgery.
  - ***We found evidence in our data to support this hypothesis. Patients who received adjuvant chemotherapy 12-16 weeks after surgery had a higher mortality hazard compared to those who received the treatment within 8 weeks after surgery (HR=1.68, 95% CI 1.12-2.51).***
- Patients who have received adjuvant chemotherapy 16 weeks or later after their surgery, or never received it will be associated with higher hazard of both overall and colon cancer-specific mortality, compared to patients who initiated adjuvant chemotherapy within 8 weeks after their surgery.

- ***We found evidence in our data to support this hypothesis. Patients who received chemotherapy 16 weeks or later or never had over two times higher mortality hazard compared to those who received the treatment within 8 weeks after the surgery (HR=2.17, 95% CI 1.62-2.91), and had an 84% increase in the hazard of colon cancer-specific mortality (HR=1.84, 95%CI 1.33-2.55).***

Hypothesis 2 (Chapter 3)

- Patients who initiated adjuvant treatment 8-12 weeks after surgery will have similar survival patterns as patients who received it within 8 weeks.
  - ***We found evidence in our data to support this hypothesis. Starting adjuvant treatment in 8-12 weeks after surgery, instead of within 8 weeks, does not appear to modify patient survival considerably.***
- Patients who have received adjuvant treatment 12 weeks or later after their surgery will be associated with higher hazard of both overall and rectal cancer-specific mortality, compared to patients who initiated adjuvant treatment within 8 weeks after their surgery.
  - ***We found evidence in our data to support this hypothesis. The adjusted analyses indicate a 37% and a 40% increase in the overall and rectal cancer-specific mortality, respectively. These clinically important differences, however, were not statistically significant.***

- Those who have never initiated adjuvant treatment after their surgery will be associated with an increase in overall and rectal cancer-specific mortality, compared to patients who initiated adjuvant treatment within 8 weeks after surgery.
  - ***We found evidence in our data to support this hypothesis. Patients who did not receive adjuvant treatment after surgery had a higher hazard of death compared to those who received it within 8 weeks (HR=1.72, 95% CI 1.26-2.37), and had a 60% increase in the hazard of rectal cancer-specific mortality (HR=1.60, 95%CI 1.11-2.31).***
- Patients who received neoadjuvant treatment will be associated with a decrease in overall and rectal cancer-specific mortality, compared to those who did not receive neoadjuvant treatment.
  - ***We did not find evidence in our data to support this hypothesis. Patients who received neoadjuvant treatment before surgery had a higher hazard of death compared to those who did not receive neoadjuvant treatment (HR=1.38, 95% CI 1.05-1.81), and had a 60% increase in the hazard of rectal cancer-specific mortality (HR=1.56, 95%CI 1.13-2.14). We believe these results are closely related with the selection criteria of patients to receive neoadjuvant treatment (discussed in Chapter 3).***

4.2 Discussion

As reported in **Chapter 2**, approximately 40% of the patients diagnosed with stage III colon cancer in Alberta between 2000 and 2005, who had surgery, did not receive adjuvant chemotherapy. Another 9% received adjuvant chemotherapy 12 weeks or later after their surgeries. These patients had more than twice as high mortality hazard as those who received chemotherapy within 8 weeks (and those who received in 8-12 weeks). That is, about half of stage III colon cancer patients in Alberta are subject to a twice or more elevated hazard of death than those who are treated in a consistent manner with the guideline.

This occurs in two ways: one is that patients fail to have a consult meeting with an oncologist after surgery (either not being referred to an oncologist or not attending the consult meeting after having been referred to); and the other is that patients do not receive chemotherapy after having a consult meeting with an oncologist (either not recommended for it by the oncologist or refusing the recommended therapy). Our previous study found that about one quarter of stage III colon cancer patients fail to have a consult meeting, while another quarter do not receive chemotherapy after a consult (1). The former is a problem of the healthcare system that can be improved. The latter can be attributable to a slow recovery from surgery and/or post-surgery complications.

Under the statistical analysis section in **Chapter 2**, I have briefly mentioned the importance of controlling for the immortal bias and the implications of not controlling for it. Due to complications after surgery, poor functional status, and/or presence of other severe diseases, some patients may

have a premature death, and therefore, they are prevented from receiving adjuvant chemotherapy within 12 weeks. If survival time is assumed to start at date of surgery, then these patients will be in the group of "did not receive adjuvant chemotherapy" for the timing to adjuvant chemotherapy variable; and we would overestimate the mortality hazard for this group. Some of these patients were not able to receive the adjuvant therapy due to their early death. The sensitivity analysis conducted in this research assessed and indicated a sensible start time of follow-up which provides unbiased estimator of HRs.

Survival of stage II/III rectal cancer patients was discussed in **Chapter 3**. We reported that 36% of the patients diagnosed in Alberta between 2000 and 2005 received surgery alone as their treatment protocol. They were mainly stage II tumor patients, with one or more serious co-morbidities, and aged 75 years or older. Recently, we reported that nearly 18% of the stage II/III rectal cancer patients, who were surgically treated, did not have a consultation with an oncologist, a barrier having adjuvant treatment (2). We must create mechanisms to detect the barriers for patients not having a consultation with an oncologist.

As a pioneer study in this area of research investigating the association between the timing of adjuvant treatment and survival among stage II/III rectal patients, we observed that patients who did not receive adjuvant treatment had a 72% increase in the hazard of death, compared to patients who received it within 8 weeks after surgery. Patients who received adjuvant treatment 12 weeks post-surgery or later and those who did not receive it were 1.40 and 1.60 times, respectively, more likely to die of rectal cancer than those who received treatment

within 8 weeks of surgery, after controlling for: stage; neoadjuvant treatment status; sex; age at diagnosis; region of residence at diagnosis; number of co-morbidities; year of diagnosis; and neighborhood-level socioeconomic factors relevant factors. Although the HR for the group who received adjuvant treatment more than 12 weeks after surgery was not statistically different from 1.0 (P= 0.15), it is a clinically significant increase and is consistent with the HR for the "no adjuvant treatment" group. The sample size included in the group who had delayed adjuvant therapy could partially explain the lack of association between timing of adjuvant treatment and survival. More investigation to identify the reasons why some stage II/III rectal patients do not receive guideline treatment is needed to optimize patient outcomes.

Chapter 3 reported a 38% increase in the overall hazard of death associated with the administration of neoadjuvant treatment, compared to those who did not receive neoajuvant treatment; and a 56% increase in the rectal cancer-specific mortality. Patients treated with pre-operative treatment (with or without adjuvant treatment) accounted for nearly 21% of all patients included in the study. According to the provincial guidelines for stage II/III rectal cancer: in cases where patients can immediately receive surgery, the administration of a short-course neoajuvant radiotherapy is not required. On the other hand, if surgery cannot be immediately offered to patients, a long-course chemoradiation therapy should be offered before surgery. This is a possible explanation for the poor survival performance among those who received neoadjuvant treatment, compared to those who did not receive it.

Despite of our robust and generalizable findings due to our population-based dataset, some limitations to our study may apply. Our linked dataset did not have information about the completeness of treatment regimen, post-surgical complications, and patient's functional status. Also, our dataset lacks information on the physician/patient perspective about adjuvant treatment preference. Preferences for receiving or not receiving adjuvant treatment is a decision that should be made in agreement between the patient and physician/oncologist, therefore, selection bias due to factors unaccounted for in the analysis may also be a limitation in this study.

4.3 Future Research Directions

Further research is needed to maximize the benefits of adjutant treatment among the colorectal patients in Alberta. Although this study represents an important source of information for both oncologists and patients, more research can be conducted to better understand the mechanisms associated with low adjuvant treatment administration, as well as treatment delays.

Some directions for future investigations are:

- To increase efforts to extend our linked database in order to capture important patient information, such as: pre- and post-surgery performance status, surgical complications, completeness of treatment, and patient treatment preferences.
- Qualitative studies could also be implemented in order to understand how patients and/or oncologist perceive the benefits and consequences of the adjuvant treatment. The findings would help researchers to build a body of knowledge about the complexity of the problem. Additionally, the information gained with would help police makers and other health care professionals to create educational and informative programs about the benefits of the adjuvant treatment.
- Knowledge translation research to disseminate, and apply in practice, our findings on colorectal cancer patient care to surgeons and oncologists who provide health services to these patients.

4.4 Conclusions

In conclusion, post-surgical stage III colon cancer patients who have received delayed chemotherapy or did not received it had an over two-fold increase in mortality hazard, compared to those who receive it within 8 weeks after surgery. Among stage II/III rectal cancer patients, those who adjuvant treatment 12 after surgery or later and those who did not receive it presented a significantly higher mortality hazard than those who receive it within 8 weeks after surgery. Although our results support the current treatment guideline for colorectal cancer in Alberta, more investigation is necessary to ensure that adjuvant treatment is provided for every patient who is clinically appropriate to receive it

4.3 References

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